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ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
01/12/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/064,000	ELIA, JAMES P.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *403-405 and 407-412* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *403-405 and 407-412* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/04/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 403-405 and 407-412 are under consideration.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 08/04/2010 has been considered by the examiner. The signed IDS is enclosed herewith. The following comments are in response to Applicant's statement of the relevance of the cited document.

3. Applicant asserts:

> As set forth at several locations in the enclosed publication, cells are a species of the genus "growth factor." Such genus/species relationship would be so recognized by one skilled in the art. Applicant believes that this evidence conclusively demonstrates that cells are a type of growth factor and thus one skilled in the art reading the term "growth factor" in the specification would understand that cells are a species of growth factors.

4. The cited document consists of a single table, which lists several cytokines, their cell sources, their cell targets, and the function performed by the cytokine. The table does not set forth that cells are a species of growth factor. There is nothing in this publication that suggests anything other than the standard usage of the term “growth factor” which is “a factor that acts upon cells” not “a factor which is a cell”.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Rejection Claims 403-405 and 407-412 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained. The rejection of record finds that the recitation in claim 403, step (b) "forming a bud" creates a lack of clarity as to whether the recited step requires action on the part of the practitioner of the method to form a bud. The most straightforward interpretation of step (b) "forming a bud", is that the practitioner is being instructed to do something. Likewise, the claim recites "(c) growing said desired artery from said bud", which also indicates that the practitioner is instructed to do something. The rejection of record finds that these instructions are unclear because the specification does not provide any teaching specifically directed to forming a bud.

7. Applicant's arguments filed 10/26/2010 have been fully considered but they are not persuasive. Applicant's response begins with a point of agreement: "The Examiner is correct in stating that the specification does not teach that a "special act" is required to form a bud or to grow an artery from said bud." This is followed by exact repetition of the arguments presented in the Brief filed 08/20/2009, which received full consideration in the Office action mailed 01/14/2010, paragraphs 4-7. Applicant's new argument begins on page 5:

> The lack of clarity posited by the Examiner in ¶7, page 5 is a product of the Examiner's refusal to read and understand the specification as well as the record as a whole. Applicant's specification recognizes that there are multiple pathways via which cell regeneration occurs--direct cell differentiation from mononuclear cells and stimulation of endogenous cells at the site of implantation are clearly described. This is consistent with the observations of the 2005 publication of Strauer et al. in Circulation at pages 1656 and 1657 entitled, "Regeneration of Human Infarcted Heart Muscle by Intracoronary Autologous Bone Marrow Cell Transplantation in Chronic Coronary Artery Disease" (hereinafter "Strauer 2005" and of record) that cell regeneration may be explained by as many as four mechanisms. There is no requirement that Applicant limit the claims to any particular growth mechanism.

8. This is not persuasive for the following reasons. First, although there is no requirement that Applicant limit the claims to any particular growth mechanism, Applicant has chosen to recite steps (b) "forming a bud…", and (c) "growing said desired artery from said bud…" The presence of these steps in the claims creates a need for clarity as to what is meant by them. Furthermore, as noted in the record, this recitation at least raises a question of the relation of the scope of the present claims to the claims of copending application Serial No. 10/179,589, which differ only by the absence of steps (b) and (c). Applicant has asserted that the copending applications are not drawn to identical subject matter because of the presence of steps (b) and (c) in the present claims. These arguments suggest that (1) Applicant intends that claims that recite a step of forming a bud (i.e. the instant claims) are substantially different from claims that recite the same step (a) without a step of forming a bud (i.e. the claims application 10/179,589) and (2) when step (a) is performed, there are instances where a bud is formed and instances where a bud is not formed. Applicant's argument regarding double patenting and argument against the rejection under 35 U.S.C. 112, second paragraph are mutually exclusive, they cannot both be persuasive. If step (b) of instant claim 403 merely recites an inherent outcome of step (a), then step (b) cannot distinguish this claim from copending claim 161, which recites an identical step (a). If step (b) of instant claim 403 is intended as a separate step in which the outcome of the step may vary depending on action taken by the practitioner of the method, then the claim is unclear because the specification does not teach this separate step.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Rejection of Claim 404 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. The rejection of record finds that claim 404, which first appeared in the record in the amendment of 11/03/2006, introduces new matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection finds no support for the combination of limitations that includes growing an artery by administration of stem cells to a damaged site in a leg of a patient in the specification as originally filed. It is agreed that the specification mentions 'injecting stem cells' for various purposes and that the specification provides support for the concept of growing an artery. The rejection of record finds that, while support for selecting these two concepts into a single method, i.e. 'injecting stem cells to grow an artery' is tenuous; the concept of first combining these limitations and then further adding the limitation of placing the cell at a damaged site in a leg of a patient is non-existent.

11. Applicant's arguments filed 10/26/2010 have been fully considered but they are not persuasive. Applicant's arguments are generally repetitive of the arguments presented in the Brief filed 08/20/2009, which received full consideration in the Office action mailed 01/14/2010, paragraphs 9-16. While the reasons of record are maintained, this response will address only particular points emphasized by Applicant.

12. Paragraphs 9-16 of the Office action mailed 01/14/2010, as well as previous iterations of the rejection of record, included extensive consideration of the concept of cells as growth factors

in view of the specification, the prior art, and the Declarations of record. Applicant objects to the emphasis on the term "growth factor" and further takes issue with the finding that there is no evidence in the record that any Declarant recognized a concept that cells are a species of growth factor in the specification as filed (Office action mailed 01/14/2010, paragraph 13):

> The present PTO Examiner's attempt to discredit Applicants teaching of using cells to promote artery growth by belatedly attacking Applicant's use of the term "growth factor" is inept. (Argument, p.8)
>
> It is clear from Paragraphs 3-7 of the Heuser declaration, for example, that declarant after reading the specification understood that Applicant contemplated implanting a growth factor comprising cells, such as, stem cells to grow an artery. This is clearly a recognition "that Declarant recognized a concept that cells are a species of growth factor in the specification as filed." (Argument, p.8)
>
> At ¶13, pages 9 and 10 of the Office Action, the PTO questions whether one experienced in the medical arts reading the specification would understand that Applicant's usage of the term growth factor was intended to include compositions comprising genes and bone marrow stem cells. Lest there be any doubt whether the answer is positive, one need look no further than Paragraphs 5-7 of the Declarations of Drs. Wheeler, Finley, and Lorincz, Paragraph 6 of the Declaration of Dr. Heuser, the Supplemental Declaration of Dr. Lorincz, and the definition found in the Alberts et al. publication definition of "growth factor" cited and made of record by the present PTO Examiner in co-pending Application Serial No. 09/836,750 and entitled, Molecular Biology of the Cell, 4th Ed., Chapter 17 (hereinafter "Alberts" and of record). Alberts' definition of a growth factor is consistent with Applicant's definition found on page 43, lines 18 and 19 of the specification, "Growth factors control cell growth, division, differentiation, migration, structure, function, and self-assembly." (Argument, p.10)
>
> Moreover, the PTO, in making restriction requirements prior to and subsequent to the date of the instant Office Action, has consistently identified genes and cells as species of the genus "growth factor". The present PTO Examiner apparently has decided to not accord full faith and credit to such PTO determinations. Accordingly, Applicant is mystified by the present PTO Examiner's insistence upon burdening the record with petty issues that were thoroughly vetted previously by the PTO, via Petition to the Commissioner in the instant application, and subsequently followed by the PTO. (Argument, p.10)

13. These assertions have been addressed in the record, especially in paragraphs 12-15 of the Office action mailed 01/14/2010, parts of which are reiterated here along with additional review of the record. First, it is important to recognize that a tenuous connection between 'injecting stem cells' and 'growing an artery' can be made without reference to "growth factors". For example, Pages 47-48 of the specification suggests that some cell selected from a germinal cell, a stem cell, and a dedifferentiated skin cell which may be used to grow an organ, which may be an artery, among other possible outcomes. If the skilled artisan makes the connection between "stem cells" and "growth of an artery", the skilled artisan then must then find the additional concept of injecting the stem cells into a damaged site in a leg of patient in order to conceive the method of claim 404. In order to support 'injecting stem cells', 'growing an artery' and 'placing the cell at a damaged site in a leg of a patient' in a single method, Applicant has argued that one of skill in the art would infer "stem cells" from sections of the specification that do not even mention any kind of cell. Applicant's basis for this assertion relies on the concept of "cells" or specifically "stem cells" as species with the genus of growth factors, as defined in the specification.

14. The record shows that Applicant's first reply in the prosecution of this case, filed 12/16/1999, dealt extensively with the scope of materials, including "growth factors", that can be used to grow soft tissue, but never once mentioned stem cells, or any kind of cell, as being among these materials. The Declarations of Drs. Wheeler, Finley and Lorincz, filed on 02/15/2001 do not mention administration of any kind of cell for any purpose; the Declarants referenced only the administration of protein growth factors or expression plasmids that encode protein factors. In fact, Drs. Wheeler, Finley and Lorincz declared to have read the same

definition of "growth factor" as in the instant specification (paragraph 5) and concluded (paragraph 7) that the Isner patent (US 5652225; of record) employed the same angiogenic growth factors as in the present application. US 5652225 discloses methods for inducing the formation of new blood vessels by administering DNA encoding an angiogenic protein—no stem cell therapies are taught. Thus, these Declarants did not suggest that they perceived any suggestion that the genus of "growth factors" was intended to include stem cells. Despite having received two Office actions on the merits, Applicant was permitted to cancel all claims and submit new claims drawn to a different invention (see the original claims, the Office actions mailed 05/27/1999, 08/16/2000, and the amendments filed 02/15/2001). Claims reciting placing a "growth factor" into a body of a human patient were introduced into this application on 02/15/2001. Applicant's Remarks filed 02/15/2001 reiterated that the Isner '225 patent teaches employing common angiogenic growth factors for causing the growth of blood vessels (p.24). The requirement for restriction/election mailed on 02/24/2004 listed twenty-four patentably distinct species (a-x) of "growth factor" were found in the instant disclosure, from which Applicant was required to elect a single product or structure. The list of species did not include "cells" or "stem cells" because "cells" or "stem cells" are never clearly set forth as species of growth factor anywhere in the instant specification. Furthermore, the claims under consideration, filed 09/18/2003, like those filed 02/15/2001, generically recited administration of a "growth factor" with dependent claims reciting "living organism", "bacteria", or "virus", but no stem cells, or eukaryotic cells of any kind, were recited. In the subsequent Office action (06/03/2004), the elected "species", "living organism", was construed according to its ordinary meaning, and the claims were rejected accordingly. The Office action acknowledged that the specification

teaches administration of cells, including stem cells, for the growth of soft tissue ("artery" was not recited in the claims), but also pointed out that the specification does not state that a stem cell should be considered a growth factor within the subgenus "living organisms" (paragraph bridging pages 7-8). This finding has been consistently held in all subsequent Office actions. Only after receiving the 06/03/2004 Office action did Applicant submit claims reciting administration of cells (08/19/2004). This marked the first time anyone involved in the application, including Applicant, ever put forth the idea that stem cells were intended to be included in the genus of growth factors as defined in the specification. Of the Declarations of record, the concept that the genus of growth factors could include cells first appeared in the Declarations of Dr. Heuser and Dr. Lorincz, filed 06/26/2006, wherein the Declarants considered newly entered claims reciting cells. So, if the term "belatedly" is applicable in this case, it should be applied to the idea that stem cells were intended to be included in the genus of growth factors as defined in the specification.

15. The Alberts definition of "growth factor" has been discussed thoroughly in the record. The Office action mailed 07/24/2007, paragraphs 14-16, included the Alberts textbook definition, medical dictionary definitions, and searches of patent and non-patent literature to show that use of the term "growth factor" to mean "a growth factor which is a cell" is inconsistent with the ordinary meaning of the term. Expressions such as "growth factors, including cells, such as stem cells" or "cellular growth factors such as stem cells" do not appear anywhere in the specification, they are never found in peer-reviewed non-patent literature, or in any patent literature, they only appear in arguments of counsel in this case and others with the same applicant; they are outside of the ordinary usage of the term "growth factor", regardless of

the academic degree held by the person using them. Furthermore, Applicant's quote from the instant specification, "Growth factors control cell growth, division, differentiation, migration, structure, function, and self-assembly" states that growth factors act upon cells, not that growth factors are cells. This is consistent with the Alberts definition of "growth factor", as well as all definitions and evidence of record. In fact, the specification consistently uses the term "growth factors" to refer to agents that act upon cells to promote tissue growth; it does not teach that cells themselves are growth factors. In view of the ways the terms "growth factors", "cells", and "genetic material" are used in context throughout the specification, there is no indication that Applicant ever intended to use these terms interchangeably, or to suggest that these distinct entities may be substituted for one another. One of many examples is found on page 46, lines 3-6 of the specification, reproduced here:

> "A variation on the theme of growing a portion of an organ is as follows: a portion of a heart dies. The pericardium is utilized as a scaffold and seeded with cells and/or genes to grow new muscle, and genes (or other genetic material) to grow new arteries".

Another example is on page 45, lines 1-3 of the specification:

> An artery can be grown in the heart, legs, or other areas by injecting a gene or other genetic material" (emphasis added)

16. This plain language from the specification shows recognition that "cells" and "genes" are distinct entities and it suggests that either cells or genes may be used to grow muscle, but only genes are used to grow an artery. Applicant's argument for descriptive support of claim 404 asserts that the specification teaches that stem cells are to be used to grow an artery, which runs counter to the plain language of the quoted text. Neither Applicant nor any of the Declarants of record have provided an explanation of why the specification should be interpreted to mean what it does not say.

17. Thus, the record shows that choice of "stem cell" as a species of growth factor was not an easy one to make; it is not explicitly taught in the specification, it was not immediately recognized by two Primary Examiners, it was not mentioned by Declarants or by Applicant until after three Office actions on the merits had been issued. It involves first selecting "cells" from within an enormous genus of asserted growth factors, and then selecting "stem cells" from within the genus of cells. Nevertheless, the line of reasoning in which a stem cell should be considered a growth factor within the subgenus "living organisms" according to the definition in the specification has been deemed sufficient to permit examination of claims that recite "cells" when the species "living organism" had been elected. This determination, dubious though it may be, has been adhered to in all subsequent Office actions.

18. No prior determination indicates that the PTO has held that a method of using stem cells for the particular purpose of growing an artery in a leg has been described. The choice of "stem cell" is only one of the selections that must be made to arrive at claim 404. The combination recited in claim 404 additionally requires the selection of "artery" from the genus of organs and soft tissues and selection of "a damaged site in a leg" from the genus of "the body" as the site where the artery is to be grown. Applicant relies of the teaching that living organisms can be growth factors (specification p. 20) and the idea that cells are organisms as justification for asserting that any time any growth factor (or gene) is mentioned, the skilled artisan is prompted to apply the teaching to cells in general, or specifically to stem cells. This leap is not justified, even in the lexicon of this specification. Applicant cannot rely upon the broad definition of "growth factor" to say that sections of the specification that mention polypeptide growth factors or genes would direct the skilled artisan to a concept of cell therapy. This leap is not justified,

even in the lexicon of this specification. Applicant is reminded that the restriction requirement mailed on 02/24/2004 listed twenty-four patentably distinct species (a-x) of "growth factor". "Patentably distinct", by definition, indicates that the species are not obvious variants of one another. It is also noted that some of the "species" are more accurately described as "subgenus". The elected "living organism" is one such subgenus which encompasses millions of distinct entities. Thus "stem cells" and "VEGF cDNA", for example, are not obvious equivalents, even if they are "growth factors". It follows that an example directed to gene therapy would not make obvious, or implicitly suggest a method of cell therapy. Any such suggestion would need to be explicitly made. As noted above, not only does the specification not make any equation of cell therapy to gene therapy, the terms "growth factors", "cells", and "genetic material" are used in the specification with no indication that Applicant ever intended to use these terms interchangeably, or to suggest that "cells" should be substituted for "growth factors" or for "genes". Therefore, the emphasis that this rejection places on the nexus between the terms "growth factor," "cells," and "genetic material" and the subject matter of claim 404 is not a "petty issue", nor does it fail to accord full faith and credit to prior PTO determinations as Applicant asserts (Argument, p. 10).

19. Applicant continues:

> Applicant notes that the present PTO Examiner has abandoned his Ruschig analysis in light of Applicant's remarks and for good reason.

20. This is not understood. Paragraph 15 of the Office action mailed 01/14/2010 cited In re Ruschig 379 F.2d 990, 154 USPQ 118 (CCPA 1967) indirectly as Ruschig was cited in Purdue Pharma L.P. v. Faulding Inc., 230 F. 3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed Cir. 2000).: "Ruschig makes clear that one cannot disclose a forest in the original application, and then later

pick a tree out of the forest and say here is my invention". In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure." Thus, Ruschig was cited for the same reason and in the same context as in previous Office actions. The mere presence of all of the limitations at various locations in the specification does not constitute adequate written description. The specification as filed does not contemplate the claimed combination of limitations. The specification does not reasonably lead the skilled artisan to the recited combination of the agent to be administered, the desired result, and the site of administration.

21. On page 7 and then in conclusion on page 11, Applicant makes similar arguments with respect to the legal standard for written description:

> The standard for written description applied by the PTO in rejecting claim 404 is tantamount to requiring the specification establish literal support for the claimed combination of features.
>
> The court in Ralston Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 227 USPQ 177 (Fed. Cir. 1985) noted that a combination of features in a claim need not exactly respond to those in the specification- the issue is whether one of skill in the art could derive the claimed combination from the specification.
> Also see In re Wertheim, 541 F.2d 265, 191 USPQ 90, 96 (CCPA 1976) wherein the court held that the claimed combination did not have to find verbatim support in the specification.

22. The rejection of record does not assert any prerequisite for literal support of the claimed subject matter. The rejection merely points out that the specification never explicitly instructs the skilled artisan to administer cells of any kind into a leg and the specification never explicitly instructs the skilled artisan to administer stem cells to form an artery. The absence of explicit teaching does not by itself indicate a lack of written description, but it does mean that the specification must provide other guidance to convey the claimed concept. It is maintained that to

arrive at the combination of limitations recited in claim 404, requires the selection of "artery" from the genus of organs, selection of "stem cells" from the large genus of growth factors encompassed by Applicant's broad definition (which, in turn, requires recognition that the definition of "growth factor" was meant to include "stem cells"), and selection of "leg" as the site where the artery is to be grown. The specification does not suggest, contemplate, or reasonably lead to the claimed combination. Even if one of skill in the art could infer the claimed method by combining the disconnected teachings of the specification, at best this would only render claim 404 obvious in view of the specification. Disclosure which merely renders the later claimed invention obvious is not sufficient to satisfy the written description requirement of 35 U.S.C. 112, first paragraph. Lockwood v. American Airlines, Inc., 107 F.3d 1505, 41 USPQ2d 1961 at 1966. The introduction of this combination of limitations in claim 404 in the amendment filed 11/03/2006 involves narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure, which is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. Therefore the introduction of this combination of limitations in claim 404 in the amendment filed 11/03/2006 constitutes new matter.

23. Rejection of Claims 403-405 and 407-412 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record. Applicant's arguments filed 10/26/2010 have been fully considered but they are not persuasive.

24. Applicant's arguments on pages 12-46 consist of a nearly verbatim repetition of the arguments presented on pages 13-50 of the Appeal Brief filed on 08/20/2009, including references to the Office Action mailed on 02/26/2009. Applicant's rationale for this duplication

is that “the relied-upon portions of the prior Office actions, if any, have not been specifically identified because the PTO simply stated that the enablement rejection was maintained "for reasons of record"”. Applicant is hereby notified that the expression "reasons of record" refers to the entire record. The introduction of new references and arguments does not imply any abandonment of prior positions. New references and arguments are generally made in addition to not in lieu of arguments of record. While reasons of record are maintained, it is still necessary to address Applicant’s arguments in each response. The Examiner’s responses to Applicant’s repeated arguments on pages 12-46 are of record in the previous Office Action mailed 01/14/2010. It is not improper for an examiner or applicant to introduce new evidence relevant to the issues while prosecution is open. The previous Office action did in fact introduce new references into the record. It would have been improper to include these new grounds in an Examiner’s Answer to Applicant's Appeal Brief. Consequently, prosecution was reopened and a Non-final Office action was written. While the references were new to the record, they were used to further explicate the reasons of record and to respond to Applicant's arguments. The same can be said for all references and arguments in the record since the present rejections were first set forth. Applicant will note that each reference and argument is related to the breadth of the claims an the amount of direction or guidance present and the presence or absence of working examples, which have been identified as the principal factors that speak against the enablement for the claims under consideration. Instances where prior positions have been modified in view of Applicant's argument, or in view of additional evidence, should not be difficult to identify. Applicant may ask for clarification or otherwise allege that the Examiner’s

position appears to conflict with earlier positions. To date, all such allegations have been found to be without merit.

25. Therefore, this Office Action will directly address arguments presented on pages 46-66 of Applicant's 10/26/2010 submission. Previous arguments are maintained but will not be repeated in this Office action except where necessary to address Applicant's remarks specifically directed to the Office action mailed 01/14/2010.

26. The rejection of record has found that the breadth of the claims and the amount of direction or guidance present and the presence or absence of working examples are the principal factors that speak against the enablement for the claims under consideration. Each of these factors has been discussed in the record. The claims are broad as they recite the administration of "stem cells", which includes embryonic stem cells, neural stem cells, amniotic epithelial cells, hematopoietic stem cells, and mesenchymal stem cells, to mention those cited in references of record. Therefore, the question of which cells would or would not work for growing an artery is critical to breadth of the claims and to enablement of the general methods.

27. Applicant begins by again taking issue with the treatment of the claims as a group and with regard to their full claimed scope:

> At page 13, ¶12 [*sic* 18] of the Office Action, the PTO confirms its position that all claims must be considered as a group, rather than individually, in the evaluation of enablement. This is patent nonsense. When evaluating enablement, it is incumbent upon the PTO to determine what subject matter each claim recites, i.e., the scope of protection sought for each claim. The scope of dependent claims are properly determined with respect to 35 U.S.C. §112, fourth paragraph. See MPEP Section 2164.08. It is clear that the Examiner's analysis did not treat the subject matter of each claim separately or treat the dependent claims according to statutory mandate.

28. All of the pending claims require administration of a stem cell at a selected site and growing a desired artery. The rejection of record finds that these elements that are essential and common to all of the claims are not enabled by the disclosure. No recited limitation rescues any

claim from lack of enablement. Therefore, each claim has been considered, but all claims are rejected on the same grounds. Therefore, this Office action will provide a single rejection and response to arguments for all of claims 403-405 and 407-412.

29. Applicant next attempts to dismiss a large section of the previous Office action:

> At pages 15-32, ¶23-47 of the Office Action, the PTO presents a series of gratuitous and disparaging remarks regarding the specification. Rather than roaming throughout the specification and then making such remarks, the PTO should read the portions of the specification that deal with the claimed invention. The PTO should keep in mind that the specification discloses numerous inventions, such as those identified in the several restriction requirements of record in the instant application. Obviously, the PTO should focus upon the portions of the disclosure related to the elected cell invention. The declarations of Drs. Heuser and Lorincz identify and then focus upon such relevant portions to evaluate enablement regarding the claimed invention. The PTO is urged to read the disclosures referenced in connection with the respective enablement opinions and then focus upon these identified, relevant portions.

30. The record shows that each of paragraphs 23-42 of the previous Office Action explicitly quotes or references an argument or assertion made by Applicant. The complaint of "roaming throughout the specification" is without merit because paragraphs 31-40 specifically address sections of the specification Applicant had selected as supporting the instant claims. Large portions of the specification were reproduced verbatim, so there can be no question of whether the specification was rendered accurately. Paragraphs 43-47 addressed sections of the specification dealing with artery formation. Does Applicant really contend that these are not relevant to the claimed invention?

31. The rejection of record has found that Applicant's specification did not disclose with specificity which cells would or would not work for growing an artery. See the Office action mailed 05/05/2008, paragraph 28; the Office action mailed 02/26/2009, paragraphs 14-16; and

most recently, the Office action mailed 01/14/2010, paragraphs 23-28. Applicant alleges a technical error in paragraph 25 (page 17):

> One of the more serious errors in the PTO's position, at page 17 of the Office Action, is that those skilled in the art at the time the application was filed understood that stem cells harvested from bone marrow and blood referred to the CD34+ fraction. There is no evidence of record supporting the PTO's position. CD34+ stem cells are a sub-fraction as evidenced by Isner. The newly submitted Fourth Supplemental Declaration of Dr. Richard Heuser (attached hereto as Exhibit A) and the Third Supplemental Declaration of Dr. Andrew E. Lorincz (attached hereto as Exhibit B), originally filed February 24, 2010, in co-pending application Serial No. 10/179,589 confirm Applicant's position. The Declarants attest that to a contrary understanding of those skilled in the medical arts, i.e. that the expression "stem cells harvested from bone marrow" is understood to refer to the entire population. Hence, the PTO's lack of understanding with the content of the knowledge of the art at the time the application was filed is demonstrated.

32. These new Declarations were signed by the respective Declarants on 01/17/2010 and 02/02/2010, and they have not been previously considered in the present application. Consideration of these Declarations is included within the context of the present rejection, as follows.

33. The Declarations of Dr. Heuser and Dr. Lorincz under 37 CFR 1.132, filed 10/26/2010, are insufficient to overcome the rejection of claims 403-405 and 407-412 based upon failing to comply with the enablement requirement under 35 U.S.C. 112, first paragraph, as set forth in the record and herein, for the following reasons:

34. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38

USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

35. There is no evidence that the experts have an interest in the outcome of the case.

36. The nature of the fact to be established is concerned with one aspect of the rejection of record in which it is found that the specification does not provide adequate guidance with regard to the choice of cells to be administered in the claimed methods. Paragraphs 7 and 8 of the Declaration are specifically directed to the scope of the expression "stem cells harvested from bone marrow" as it would be understood by a person of skill in the art at the time the application was filed in 1998. Therefore, the Declarations are most relevant to claims 407 and 408, which are the only pending claims which recite "stem cells harvested from bone marrow".

37. The Declarants in paragraph 7 express an understanding "that it was commonly known at the time of the Elia invention, April 21, 1998, that bone marrow comprise stem cells that are pluripotent in that they are capable of forming multiple tissue types." This is not disputed. The Declarants stress in paragraph 7 that it is not possible to cause artery formation by implanting only CD34+ endothelial progenitor cells into a human patient because CD34+ endothelial progenitor cells are unipotent and do not differentiate into smooth muscle cells. In paragraph 8, the Declarants express an "understanding that as of circa the date of the Elia invention those skilled in the medical arts did not limit the scope of the term bone marrow stem cells to a subset of mononuclear cells composed of CD34+ endothelial progenitor cells." This understanding is not disputed. The record in this case does not include any suggestion or allegation that the term "bone marrow stem cells" should refer only to a subset of mononuclear cells composed of CD34+ endothelial progenitor cells.

38. In paragraph 8, the Declarants express an understanding that "the language "stem cells harvested from bone marrow" as defined in the written disclosures above-mentioned patent applications and claims to encompass the entire population of bone marrow mononuclear cells and cellular components, including a range of cytokines, in contrast with any fractionated population of such cells." Declarants further express the opinion "that one skilled in the medical arts reading the application at the time of filing, April 21, 1998, would have understood that the language was intended to describe a composition comprised of the entire population of bone marrow cellular components. To conclude otherwise, specifically in the absence of explicit direction to conduct a fractionation of cells, would require such a skilled person to ignore the decades of use of such language in the medical arts, particularly in regard to the practice of treating patients with bone marrow transplants".

39. Opposing evidence has been discussed on the record. It has been acknowledged that the instant specification does not teach that there is anything critical about how to prepare bone marrow stem cells (paragraph 15 of the 02/26/2009 Office Action and paragraph 27 of the Office action mailed 01/14/2010). The issue is what effect this absence of explicit direction would have on the guidance perceived by one of skill in the art reading the specification. A point made in the rejection of record, but not addressed by the Declarants, is that the manner in which bone marrow stem cells are discussed in the specification logically teaches away from any suggestion to use unfractionated bone marrow for any purpose. It is again emphasized that **the instant specification refers to bone marrow only in the sentence, "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques"**, which appears three times (page 40, lines 27-28; page 41, lines 23-24; page 42, lines 9-10). Thus, the specification suggests that three sources of stem cells are equivalent to one another for purposes of the disclosed methods. How can one logically separate "from the bone marrow", "from the

blood", and "from cell culture techniques" when these distinct sources are always tied together in a single sentence? (The fact that the examples in which this sentence appears are not directed to artery formation is a separate issue addressed elsewhere). **This equivalency is asserted in pending claims 407 and 409, which respectively recite living stem cell harvested from the bone marrow and the blood of the patient, as alternatives for the purpose of growing an artery.** The record shows, however, that these cell populations are not equivalent to one another. It was still unclear long after the instant specification was filed whether circulating blood contains any mesenchymal stem cells or other marrow-derived cells with broad potential (Roufosse et al., Int J Biochem Cell Biol. 2004 Apr;36(4):585-597 of record; see especially section 3, pp. 588-591, Table 2, and section 6, p. 394). Therefore, by listing "stem cells harvested from the blood of the patient" as an equally usable alternative of "stem cells harvested from the bone marrow", the specification teaches away from any suggestion that the "stem cells" of the claims must necessarily include mesenchymal stem cells. The instant specification does not mention mesenchymal stem cells, even once. It also follows that "stem cells harvested from the blood" differ from "stem cells harvested from the bone marrow" at least by the absence of mesenchymal stem cells. If the specification teaches that "stem cells harvested from the blood of the patient" are equivalent to "stem cells harvested from the bone marrow" for purposes of the claimed methods, and it is known in the art that blood does not comprise the complete set of pluripotent cells found in marrow, it is illogical to conclude that the specification intends "stem cells harvested from the bone marrow" to mean the "entire population of bone marrow mononuclear cells and cellular components, including a range of cytokines". That is, if "stem cells harvested from the blood of the patient" are sufficient to grow an artery, then why would

anyone infer that the "entire population of bone marrow mononuclear cells and cellular components, including a range of cytokines" is required, or preferred, or even suggested? The specification and claims would make sense if "stem cells harvested from the bone marrow" is understood to refer to only those cells from bone marrow which can also be found in blood, such as, for example, the CD34+ population known at the time of filing to include hematopoietic stem cells.

40. The possibility should be considered that in casual conversation, or in situations where precision is not needed, persons of skill in the art may refer to a "stem cell transplant" when the actual procedure under discussion employed unfractionated bone marrow or the entire mononuclear fraction. Conversely, one might casually say "bone marrow transplant" when the patient actually received only mononuclear cells or selected stem cells. This would account for the Declarants' stated conclusion despite the logical inconsistency described above. In this view, it is plausible that Applicant had unfractionated bone marrow in mind when writing "stem cells harvested from the bone marrow". Other than the instant specification, no examples of such imprecise language have been made of record, however. The evidence of record does include examples which show that when details matter, it is common practice to use a generic term such as "bone marrow" or "bone marrow cells" when little or no fractionation is done, and to use the term "stem cells" when referring to the actual stem cell population. For example, when Janssen et al., (Journal of Hematotherapy, 1:349-359 (1992); of record) describe use of an apparatus for processing of bone marrow stem cells, the definitive demonstrations that "stem cells" were obtained were by identification of CD34+ cells or by colony forming assays; prior to that the cells were simply referred to as fractions obtained in a step of isolation (mononuclear, Ficoll

gradient, buffy coat, etc., see Figures 10 and 11 and Table 1). The claims of the Kornowski '832 patent of record recite administration of bone marrow aspirate to induce collateral blood vessel formation in the heart (see claim 1). Similarly, Strauer (2002, of record) acknowledges that bone marrow contains stem cells, but uses the generic term "bone marrow cells" to describe the population of bone marrow mononuclear cells used for transplantation (see Abstract and text on page 1913). Applicant has repeatedly asserted that the instant specification teaches administration of the same cell population used in the Kornowski patent and the Strauer publication. It is noted that "bone marrow aspirate" is not synonymous with "bone marrow mononuclear cells" as mononuclear cells are obtained by a step of gradient fractionation (see Janssen et al.; see also Strauer, p. 1914, left column). Similarly, Applicant has asserted that the Dohmann reference of record discloses the process, materials, and results which correspond to the claimed invention. Dohmann administered "autologous bone marrow mononuclear cells" (see title). It is clear that Kornowski, Strauer, and Dohmann were precise in their descriptions and they did not use a term that denotes a subpopulation of cells (stem cells) when they were trying to communicate that little or no fractionation was performed.

41. Finally, there is a question of the presence or absence of factual support for the expert's opinion. Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949). All of the arguments, evidence, and references cited above were available to the Declarants prior to the dates the Declarations were signed. The Declarants did not specifically address any of the arguments, evidence, and references of record, nor did they offer any factual evidence to support their expressed opinions. Even if published examples which conform to the Declarants' opinions, i.e. wherein the

expression “stem cells harvested from the bone marrow” means “entire population of bone marrow mononuclear cells and cellular components, including a range of cytokines”, were to be found, this would not negate the point made in the rejection. The evidence of record establishes that at least some persons of skill in the art carefully distinguish "stem cells" from “the entire population of bone marrow cellular components" when they aim to provide information that would enable others to reproduce their results. Therefore, in the absence of further explanation or a working example, the expression “stem cells harvested from the bone marrow” does not clearly guide the skilled artisan to choose either unfractionated marrow or the mononuclear fraction. Thus, the declarations have been fully considered and the rejection is properly maintained based on consideration of the preponderance of the totality of the evidence.

42. Applicant next alleges error in paragraph 27 (page 19):

> An adjunct to this serious technical error is the PTO's highly erroneous assertion at page 19 of the Office Action is that CD34+ endothelial progenitor stem cells can produce artery growth. The above-mentioned declarations demonstrate error in this aspect as well.
>
> In connection with the present PTO Examiner's erroneous analysis that CD34+ cells alone function to form arteries, at page 19 of the Office Action, the present PTO Examiner makes the nonsensical statement that Applicant could take a contrary position and argue such position. Applicant has not urged any such result and, in fact, the present PTO Examiner's position is not factually sound. This spurious "issue" is a prime example as to why the present record has become so lengthy.

43. The language in question is reproduced here:

> In view of the vague teaching of the specification, Applicant could devise an argument to fit any subsequent disclosure. That is, if it had turned out that the CD34+ population of stem cells was sufficient to promote artery growth, Applicant could claim to have predicted that outcome by arguing that, of course, use of the CD34+ population is implicit in “stem cells harvested from bone marrow, the blood of the patient, or from cell culture techniques”. Such argument would have equal validity (or lack thereof) to the argument Applicant is presently making.

44. It should be clear that it is Applicant's description that is not factually sound. This passage does not include any assertion that CD34+ endothelial progenitor cells can produce artery growth. The point made in paragraphs 26-28 of the previous Office action, to which Applicant does not respond, is the contrast between references of record and the instant specification. The cited references exemplify careful use of terminology, coupled with actual demonstrations of how the cells were prepared and the outcomes that were achieved, whereas the instant specification does not give the skilled artisan clear instructions for what to do. While Applicant as argued that "The failure of the specification to teach separating and excluding any given fraction of mononuclear bone marrow stem cells is consistent with the requirement for using an unfractionated bone marrow composition and constitutes a reasonable reading of the specification", such teaching would be equally consistent with a requirement for CD34+ stem cells. Applicant may argue for either broader or narrower focus, depending on the perceived need during prosecution, and still find something in the specification that can be construed to support the argument, provided one does not care about the meanings of words. However, when it comes to actually practicing a method, the specification does not tell the skilled artisan what to do.

45. Applicant next takes issue with a particular instance where the specification has been found to lack clarity:

> At page 28, ¶40 of the Office Action, the PTO characterized the term "cascade of genetic material" as a malapropism.

Applicant then presents a quotation from The Journal of Invasive Cardiology, Vol. 17, July 1, 2005, in which Dr. William O'Neil makes reference to "the cascade of the processes that actually allow a new cell to come in and regenerate." From this, Applicant argues:

> Such quotation is evidence that those skilled-in the medical art reading the specification would fully understand which cells are intended and the methodology for implanting such cells as well as the terminology used by Dr. Elia in describing the necessary in vivo cascade of processes that allow implanted cells to regenerate in a patient's body. Prior to deeming the term to be a malapropism, the present PTO Examiner deemed such term to be nonsense. Apparently Dr. O'Neil was able to educate the present PTO Examiner to the extent that the term is no longer nonsense. Moreover, there are other versions of this well known medical terminology in the record of this and co-pending applications of Dr. Elia that are not exactly the same as used by Drs. O'Neil and Elia. Perhaps the present PTO Examiner can educate Applicant as to which of these versions are malapropisms and explain why this is the case. Such non-relevant "issue" is simply another reason as to why the instant record has grown to such length

46. First, it should emphasized that the terminology of the specification is a relevant issue because of the statutory requirement that the specification should set forth a description of the manner and process of making and using the invention, "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same". Applicant has requested explanation, and so such explanation will be provided, again. The expression "cascade of genetic material" has been addressed thoroughly in the record. Applicant is referred to the Office action mailed 07/24/2007 at paragraphs 19-22. The characterization "malapropism' is not a change from the original "makes no sense", but instead is a further explanation of exactly why the expression "cascade of genetic material" is considered to make no sense. Applicant's current argument is rooted in Applicant's continued refusal to recognize the difference between "material" and "processes". In biology or medicine, a "cascade" is "series of reactions" or a "series of steps, each step being triggered by the preceding one". This is exemplified in the cited quote from Dr. O'Neill, and also in the Augustin reference of record, each of which refers to a "cascade of processes." However, the fact that Drs O'Neill and Augustin can appropriately use the term "cascade" does not change

the instant specification. The specification does not describe an in vivo cascade of processes but instead refers to a "cascade of genetic material". "Material" does not mean "reactions", "steps", or "processes". In contrast to "genetic cascade", the expression "cascade of genetic material" evokes an image of a DNA preparation being spilled from the laboratory bench. It is agreed that one of skill in the art might be inclined to guess that Applicant really meant something like "genetic cascade" or "cascade of genetic processes" instead of "cascade of genetic material". However, the need to ignore such misapplication of terminology detracts from the clarity required by the statute. Most importantly, the rejection of record has consistently maintained that even if the malapropism of "cascade of genetic material" is ignored and the expression is taken to be equivalent to "genetic cascade", this expression does not provide any useful guidance as to how to use stem cells to grow an artery.

47. Applicant next argues:

> At pages 29 and 30, ¶¶41 and 42 of the Office Action, the PTO again questions how to use stem cells to grow an artery. The simple answer provided by the specification is to place such cells into the body of a human patient by, for example via injection. The body then completes the process, as disclosed in the specification, by growing an artery via direct differentiation and morphogenesis along genetically predetermined pathways. Such process is remarkably simple from a medical standpoint once the inventive concept is disclosed.

48. Applicant's argument is not persuasive because it suggests that bone marrow stem cells can be made to spontaneously form any desired organ simply by placing them in the desired location. This idea has no support in the long history of bone marrow transplantation. This was addressed in ¶¶41 and 42 of the previous Office Action, which pointed out that Applicant relies on the notion that, because the specification (e.g. pages 40-42 and 47-48) suggests the growth of organs which comprise an artery, the specification teaches how to grow an artery. These same

pages of specification which Applicant relies upon also teach that an organ encompass growth of pancreatic islet cells or a heart (specification p.48, lines 3-4), a tooth, a kidney, or an eye (specification, pages 40-42). If stem cells can do all of these things, how does one control the process to specifically form an artery? Apparently, according to Applicant's argument, one grows an artery, as opposed to pancreatic islet cells or a heart, simply because in these claims, an artery is desired at the location where the cells are injected.

49. Applicant continues:

> In this regard, the PTO's citation of a page 45, lines 1-4 is noted. Of course, because genes are mentioned, one skilled in the art would recognize that cells could be likewise employed to grow an artery.

50. As previously noted, the specification, at page 45, lines 1-4, specifically teaches administration of materials other than cells for the purpose of growing an artery:

> An artery can be grown in the heart, legs, or other areas by injecting a gene or other genetic material into muscle at a desired site.

Similarly, later in the same paragraph, page 45, lines 13-14:

> VEGF proteins can be made in a lab and injected into a patient intravenously, intraluminally, or intramuscularly to promote the growth of an artery.

Other similar teachings have been pointed out in the record, for example, Page 46, lines 3-6:

> "A variation on the theme of growing a portion of an organ is as follows: a portion of a heart dies. The pericardium is utilized as a scaffold and seeded with cells and/or genes to grow new muscle, and genes (or other genetic material) to grow new arteries".

As noted previously, this plain language from the specification shows a recognition that "cells" and "genes" are distinct entities and it suggests that either cells or genes may be used to grow muscle, but only genes are used to grow an artery.

Page 52, lines 17-19:

> Gene products can be inserted in a patient's body to produce an organ or other structure. For example, VEGF growth factor inserted in the body produces an organ, i.e., an artery.

51. Therefore, numerous sections of specification teach that "genes", "genetic material", "gene products", or "proteins made in the lab" may be administered to promote growth of an artery, with no mention of "cells", except as the targets of action. These sections of the specification do not even contribute to the concept of administering stem cells to grow an artery, much less provide enabling guidance for the method. Thus, Applicant's assertion that "Of course, because genes are mentioned, one skilled in the art would recognize that cells could be likewise employed to grow an artery" requires the skilled artisan to reach a conclusion that is directly and explicitly contradicted by the plain language of the specification.

52. Applicant next attempts to dismiss another section of the previous Office action:

> At page 30, ¶44-47 of the Office Action, the PTO erroneously states that the stated goal of the claimed method includes "growing a new artery." Such identified "goal" does not appear in the claims, and thus the present PTO Examiner is in error. Being that such premise is in error, the comments in ¶¶45-47 are likewise not relevant to the claims under examination.

53. Of course, the claims under consideration do not recite the word "new". However, as "new arteries" are a subset of "arteries", it is accurate to say that the stated goal of the claimed method includes "growing a new artery". Therefore, ¶44-47 of the previous Office Action are relevant to the claims under consideration. By teaching that new arteries, or sections of arteries, will grow adjacent to existing arteries and subsequently integrate, the instant specification teaches a novel process that is at odds with the prevailing understanding in the art. Therefore, in addition to the fact that prophetic Examples 18, 19, and 36 do not teach that cells should be administered to grow and artery, these Examples are not credible in the absence of a demonstration that such results did or would occur in vivo. Furthermore, although post-filing

publications describe methods and results that fall within the scope of the claims under consideration, none of these references support or suggest anything like the formation of a new artery structure which then integrates into an existing artery as taught in the specification. Therefore, no assertion that any post-filing reference confirms Applicant's disclosed and claimed results can be found persuasive if formation of a "new artery" is defined as in the specification at pages 54, 56, and 62.

54. Pages 54, 56, and 62 are within Examples 18. 19, and 36, which prophetically describe introduction of VEGF cDNA into a patient to induce angiogenesis. On 05/25/2007, Applicant entered into the record a method for extrapolation of dosages of a VEGF cDNA construct taught in Examples 18. 19, and 36 to calculate a number of stem cells to use in a method wherein stem cells are used in place of the cDNA construct, accompanied by declarations by Drs Lorincz and Heuser. Applicant next addresses said method:

> At pages 32-37, ¶¶48-55 of the Office Action, the PTO continues to critique a conversion technique that has been in existence in the medical field for a long period of time. In rebuttal, the PTO is referred to Applicant's above remarks involving this issue, as well as those presented below.
>
> If the present PTO Examiner wishes to improve such well known and employed conversion technique, Applicant is sure that the medical field would welcome any improvement. However, the use of such calculation to demonstrate dosage conversions has between demonstrated twice by Applicant and confirmed to be reasonable by medical experts Drs. Heuser and Lorincz. Such evidence should put an end to this issue, especially since the present PTO Examiner has not introduced any evidence and thus appears to have engaged in puffery.
>
> In any event, the PTO's ad hominem criticism of Applicant's conversion set forth at fails to adequately give weight to its evidentiary value.

55. Every assertion in the above two paragraphs has been shown to be incorrect in the Office action mailed 07/24/2007 at paragraphs 35-42, the Office action mailed 05/05/2008 at

paragraphs 34-38, and the Office action mailed 02/26/2009 at paragraphs 24-28, and most recently in the Office action mailed 01/14/2010, paragraphs 48-55, to which Applicant now responds. First, the record shows that Drs. Heuser and Lorincz **did not** state that the conversion method under discussion has been in existence in the medical field for a long period of time: the Declarants carefully stated that the conversion method "is consistent with the extrapolations that have been performed for over 50 years." It has been shown in the record that the "consistency" extends only to the point that the extrapolations involve math and DNA; any further comparisons would be impossible. The record shows that the calculation under discussion **is not** "a conversion technique that has been in existence in the medical field for a long period of time"; it is not substantially analogous to well known methods of converting DNA amounts to cell numbers within a species cited by the Declarants. Evidence to support this conclusion **has been** introduced. Applicant is again referred to the Office action mailed 07/24/2007 at paragraph 38, wherein an online publication titled Plasmids; Histories of a Concept, was cited to establish that the term "plasmid" was coined in 1952. It was further pointed out that techniques for making cDNA (copy DNA made by reverse transcription of mRNA), and for using plasmid vectors propagate and express cDNA in cells were developed in the 1970s. Therefore, contrary to Applicant's assertion, it is well established by objective evidence that scientists 50 years prior to the filing date of the instant application (the time period cited in the Declarations filed 05/25/2007 at paragraph 6) would not recognize the terminology or even imagine the concept of the conversion under discussion. For another example, the quantitative and qualitative differences between a plasmid construct and genomic DNA as it is found in cells have been discussed, e.g. the Office action mailed 02/26/2009 at paragraph 25. Plasmid DNA constructs are

drastically different from cellular genomic DNA with respect to their gene dose per mass, and because they contain DNA derived from different species. It has been shown, using the data from tables supplied by Drs. Lorincz and Heuser, and the primary, peer-reviewed publication that first described the phVEGF$_{165}$ plasmid (Isner et al., Circulation. 1995; 91:2687-2692; of record) that the amount of VEGF coding sequence in an equal mass of human genomic DNA and VEGF plasmid DNA differs by a factor of more than 5 x10^5. Paragraph 37 of the 07/24/2007 Office Action pointed out further differences between plasmid constructs and cellular genomic DNA which had been brought to the attention of the Declarants, but which were not addressed in the Declarations. Applicant has not refuted these findings. The use of such calculation to demonstrate dosage conversions has **not** been demonstrated twice, or even once, by Applicant. Here Applicant appears to be referring to Applicant's attempt to support the conversion method using data from the Strauer 2002 reference and the Isner '887 patent (see pages 30-31 of the Appeal Brief filed 08/20/2009). Neither reference teaches or suggests that the amount of plasmid DNA should was used as a guide for the amount of cells to use in cell therapy. Strauer does not mention plasmids at all. As shown in paragraph 53 of the Office Action mailed 01/14/2010, Isner teaches a 4000-fold range of μg DNA and a trillion-fold range (10^6 to about 10^{18}) of cells. This shows that even if using the amount of plasmid DNA to calculate a number of eukaryotic cells were a legitimate procedure, the formula for doing so based on Isner's numbers would not be the simple ratio Applicant has presented. This supports the rejection of record, which finds that any relationship between the results of Applicant's formula and any cell number taught in Isner '887, or in any post-filing art, is coincidental. It is neither surprising nor convincing that a formula could derive a value within the trillion-fold range of cells taught by Isner.

56. Thus, the "evidentiary value" of Applicant's conversion is as follows. It is clear from the facts presented in the rejections of record, that the method under discussion, which purports to extrapolate an appropriate cell number for administration from the quantities of plasmid DNA, is Applicant's post hoc derivation. It is not present in the application as filed. It is not implicit in the teachings of the specification. It is not substantially analogous to the well known methods of converting DNA amounts to cell numbers within a species cited by the Declarants. It is not information that is already known by those skilled in the medical arts. There is no example of it in the prior art or post-filing art. The present rejection, as originally set forth, did not specifically mention the absence of guidance as to how many stem cells should be used to grow an artery. Cell dose has never been cited as single, critical factor for determining enablement. Applicant has argued that stem cell overdosing has not proved to be problematic and that safe dose ranges have been established over years of medical practice directed to bone marrow transplant cell therapy. Therefore, the conversion method does address any specific point that has been deemed to be critical for enablement. In the face of this, one might ask why Applicant has chosen to bring the calculation into the discussion. The answer appears to be that Applicant seeks to persuade the Examiner, or the Board, that the specification is far more definitive in its teaching than it actually is. The record (see Office Action mailed 07/24/07, paragraph 35) shows that Applicant entered the calculation and the associated Declarations into the record of this application on 05/25/2007, after the evidentiary value of the same calculation method had been rejected in copending application 10179589. In the '589 Application, Applicant had represented as fact the following statement in the Remarks filed 08/28/2006, page 9:

> Applicant's specification describes artery growth and heart repair by direct injection of growth factor cells in dosage ranging from approximately 6.25 x 10^6 (Example 17) to approximately 12.5 x 10^6 (Example 18).

Applicant repeated the same assertion in the Remarks filed 05/29/2007, paragraph bridging pages 18 and 19. (Examples 17 and 18 in the '589 application respectively correspond to Examples 18 and 19 in the present application). In this regard it is noted that in continuation application 09/794456, Applicant has three times represented as fact the same assertion that the specification discloses specific results based on the extrapolation:

> "Appellant's specification describes new artery growth and heart repair by direct injection of growth factor cells in dosage ranging from approximately 6.25 x 10^6 (Example 18 & 36) to approximately 12.5 x 10^6 (Example 19)" (09/794456 Response filed 06/26/2006, page 74; Appeal Brief filed 02/08/2007, p.22; Appeal Brief filed 04/17/2009, p. 28).

In view of this background, Applicant's present assertion that, "There is neither need nor requirement for the instant specification to disclose the challenged conversion" (Argument p. 51) in untenable. The record is clear that the 6.25 x 10^6 and 12.5 x 10^6 cell numbers do not appear in the specification, the method for deriving these cell numbers is not in the specification, Examples 18, 19, and 36 do not mention cells of any kind, and so they cannot suggest to the skilled artisan that one should even try to calculate a number of stem cells. Therefore, Applicant's conversion method has no "evidentiary value" in favor of enablement of the claims under consideration, and its only potential value is to create an appearance that the specification teaches something that it plainly does not teach.

57. The charge of ad hominem argumentation is serious because such arguments are usually considered to be invalid:

> Ad hominem 1.(logical fallacy) A fallacious objection to an argument or factual claim by appealing to a characteristic or belief of the person making the argument or claim, rather than by addressing the substance of the argument or producing evidence against the

> claim; an attempt to argue against an opponent's idea by discrediting the opponent himself. 2. A personal attack. (From: http://en.wiktionary.org/wiki/ad-hominem).

58. The record does not support Applicant's description of the criticism of record of Applicant's conversion as ad hominem. It is acknowledged that the present Examiner has been purposefully blunt in considering the adequacy of the specification to support the pending claims. However, no argument or assertion has ever been made that the specification is inadequate, or that any argument is not persuasive, because of any characteristic of the person who wrote the specification or made the argument. Even the admittedly harsh expression "stumbled upon" was not directed to Applicant as a person, as the context clearly shows that subject at hand was the coincidental nature of the relationship between the results of Applicant's formula and the cell numbers taught in Strauer. It is reiterated that the finding are not based solely on the Examiner's opinion, but are supported by facts and references. The subject of ad hominem argumentation will again be addressed in this Office action, as it relates to all of the Declarations of record.

59. Paragraph 57 of the 01/14/2010 Office Action cited Ziegelhoeffer to argue that the prediction that ""if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro" (specification p.48, lines 13-15) has been shown not to be true when the source of stem cells is a mixed population of bone marrow cells and the organ under consideration is a new artery." Applicant responds:

> At pages 38 and 39, ¶¶56 and 57 of the Office Action the PTO takes issue with Applicant's explanation in the specification that the mechanism for artery growth involves differentiation and morphogenesis. The mechanism of artery growth is not contained in the claims and it is trite law that an applicant is not required to identify, or

> be correct if identification is made, the mechanism by which an invention operates. It is sufficient, as noted earlier, that Applicant describes multiple mechanisms in the specification for growing soft tissue, such as arteries, which are organs.

60. Applicant's remarks regarding a requirement for identifying a mechanism of action are not disputed. Nevertheless, the issues raised in paragraphs 56-57 of the previous Office action are relevant to the predictability in the art, to questions of whether post-filing reference confirm the teachings of the specification, and to the persuasiveness of Applicant's prior arguments. Applicant disparages the Ziegelhoeffer reference because it relied upon an animal model. It is evident that the editors of "Circulation Research, Journal of the American Heart Association" deemed the Ziegelhoeffer study sufficiently relevant to human conditions to be worthy of publication. Applicant further points out that pages 1656 and 1657 of Strauer 2005 teach that

> "multiple mechanisms (multifactorial) are involved with the regenerative potential of bone marrow - derived stem cells and include direct differentiation as well as the stimulation of endogenous stem cells, etc. which are responsible for cell-biologic and molecular mechanisms resulting in organ growth for human beings…Strauer 2005 specifically points out that the precise mechanism for artery growth is undeterminable."

All of this attests to the unpredictability of biological processes, which is particularly important in determining enablement under 35 USC 112(1). In this regard, Applicant's previous quote from Dr. O'Neill is apt:

> in terms of the degree of our ignorance about the basic science in this area. My own feelings is that God - or nature - in His infinite wisdom, is a lot smarter than we will be for a few centuries yet in terms of the cascade of the processes that actually allow a new cell to come in and regenerate.

In contrast to Dr. O'Neill's humble expression, Applicant had argued repeatedly, and with certainty, that stem cells are able to promote tissue growth or formation of an artery through "differentiation and morphogenesis", as documented in paragraph 56 of the previous Office action. Applicant's present argument may be convincing to the point that direct differentiation

has not been disproved when the source of stem cells is a mixed population of human bone marrow cells and the organ under consideration is a new artery in a human. However, in view of the uncertainty and lack of knowledge in the field, Applicant's repeated reliance on "differentiation and morphogenesis", supported by a single sentence in the specification, p.48, lines 13-15, does not make for a convincing argument that post-filing disclosures confirm the teachings of the specification.

61. Paragraphs 58-62 of the previous Office action addressed the Strauer 2002 reference of record, as it provides post-filing evidence of experimentation. Applicant responds by reiterating arguments that were previously addressed:

> At pages 40-42, ¶¶58-62 of the Office Action, the PTO again relies upon Strauer as evidence that the more than routine experimentation would be required to practice the claimed invention. Applicant disagrees. In the Office Action, the PTO apparently takes the position that the mere designing of the Strauer trial regarding cell population, administration technique, and transplantation timing somehow constitutes evidence of undue experimentation. However, when challenged previously, the PTO could not point to any experimentation actually performed by Strauer, for good reason. This latest position by the PTO regarding Strauer constitutes a further change of the explanation regarding the evidentiary value of this publication. The PTO apparently has relied upon Strauer as establishing that a determination of cell population is critical, citing pages 1916-1917 of the publication. The PTO fails to point to any specific teaching in the record, which supports this proposition, and for good reason.
>
> The present PTO Examiner previously asserted in co-pending applications that, "...considerable experimentation was done, if not by Strauer, then by others in order to determine the effective cell population" without citing any instances of experimentation. Such statement serves as an admission that Strauer performed no experimentation, and thus directly contradicts the statements regarding Strauer in the Office Action.
>
> Strauer--just like Applicant---does not disclose that stem cell population is critical and does not describe any experimental protocol for selecting and isolating certain cells from the entire cell population described for the treatment therapy. Strauer does not describe using any experimental protocol to determine appropriate cell population, i.e., there is no requirement for using a specific subset of bone marrow stem cells. Regarding time of treatment, Strauer does not disclose that determining time of treatment required experimentation.

62. The Office Action mailed on 02/07/2007 included the following on pages 9-10:

> 1) In the instant case, the quantity of experimentation required would be very large. Applicant's attention is directed to pp. 1916 to 1918 of Strauer (of record, 2002, Circulation 106:1913-1918), who review the crucial questions that had to be addressed while designing and realizing their trial of administering stem cells to human patients to repair damaged heart tissue. These included decisions regarding what cell population to use, what delivery method to use, and when cells should be transplanted. As can be seen from pp. 1916-1918, these were not simple or routine matters and involved great quantities of experimentation. In fact, one can see that the determinations of these details involved the act of invention.
> 2) The specification provides no guidance along the lines of the details worked out by Strauer.

63. In view of the above, it is difficult to understand why Applicant would say "In the Office Action, the PTO now apparently takes the position that the mere designing of the Strauer trial regarding cell population, administration technique, and transplantation timing somehow constitutes evidence of undue experimentation" and "This…constitutes a further change of the explanation regarding the evidentiary value of this publication"(Argument pages 52-53) as if this position were something new or contradictory to the record. These same grounds with respect to the Strauer references have been maintained throughout all prosecution for the past 4 years.

64. Contrary to Applicant's repeated assertion, 58-62 of the previous Office Action did point to a specific teaching in support of the proposition the Strauer considered determination a cell population to be critical—see the quote from Strauer, p.1916 in paragraph 61, which explicitly lists "What cell population should we deliver?" as the first of 3 crucial questions to consider. Note also that this same teaching was cited in the Office Action mailed on 02/07/2007, quoted above. Strauer similarly identified "When should the cells be transplanted?" as a critical question. Paragraphs 58-62 made the point that Strauer et al. explicitly disclosed their reliance upon the prior work of others. Multiple publications were cited by Strauer pointing to the prior

work that was considered in the selection of cell population and determining the timing of cell administration. (Of course, the experimentation relied upon was "prior" to the Strauer study, but "post-filing" relative to the instant application). Applicant's arguments rely on the untenable position that the basic and preclinical studies cited by Strauer do not represent experimentation. It cannot be disputed that published scientific papers represent actual experimentation and that when work based on actual experimentation is reported in a scientific journal, not every detail from the laboratory notebook makes it into the final draft. This remains important in considering whether Strauer constitutes evidence of extensive experimentation. The recognition that work was done by others is not a contradiction of any previous statement. It does not matter whether Strauer et al. performed the preclinical experimentation or the work was done by others. What matters is that the successful method relied upon experimentation, and it could not be carried out on the basis of the mere suggestion that "a patient's own cells" may be used to form an artery, among other possible outcomes (Specification, pages 47-48). Likewise, it does not matter whether Strauer ultimately found that "there is no requirement for using a specific subset of bone marrow stem cells" or that a broad range of timing of cell administration after damage to the heart is permissible. These conclusions were reached only in view of Strauer's results and the work of others cited by Strauer, and they were not predicted by the assertion that "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques" can be genetically engineered to form entire organs such as a tooth, kidney, or eye, depending on the genes used (Specification, Examples 11-17).

65. The Office action mailed 02/26/2009 cited two internet articles published in The Journal of Invasive Cardiology, Vol. 17, July 1, 2005, which were again addressed in paragraphs 63-65

of the 01/14/2010 Office action. In response Applicant repeats previous allegations that full consideration of the publications would not support the findings of the rejection of record. Applicant further reiterates comments made response in the cited articles. These comments, individually or taken together, do not overcome the essential findings related to the articles. It remains true that the concerns addressed by the participants in these discussions that took place about seven years after the instant specification was filed are the same as those raised herein and in the rejections of record with respect to the lack of guidance provided by the instant specification. It is clear that questions of choice of cell, dosing, timing, means of delivery, and cell survival, were still unanswered in these discussions. It remained uncertain what the critical cell in the preparations administered in the intervening art is; it may not be any previously characterized stem cell, it may not even be a stem cell at all but rather some other previously uncharacterized growth factor secreting cell. The wisdom of transplanting an uncharacterized mixture of cells was in question (see comments by participants O'Neill, Dangas, and Holmes). The net effect of the multiple uncharacterized factors secreted by transplanted cells was still unknown and considered to be unpredictable (see comment by participant Dangas). Participant Witlow's comments are noteworthy if the selected site for growth of a desired artery is the heart and in view absence of any specific guidance as to how many cells to deliver in the instant specification; the non-toxicity of administered cells is apparently not predictable in the situation of attempting to repair a damaged heart, regardless of whether Dr. Witlow's concerns are ultimately substantiated or dismissed. These questions remained even though the participants were well aware of post-filing disclosures of record; Strauer was specifically cited. Clearly, considerable experimentation had taken place. Several participants suggested that more

experimentation was needed, including Dr. Richard Heuser, a Declarant of record in the instant case.

66. While Applicant's present arguments were generally addressed in the previous Office action, the following statements warrant further consideration:

> Dr. Pollman from Guidant Corp. described the BOOST method, "as a simple syringe injection system loaded with 10 cc of bone marrow, 3 cc of which is applied to the coronary arteries." Dr. Pollman does not indicate that any further manipulation was necessary.
>
> Dr. ONeil's third question virtually confirms Applicant's argument that the specification teaches using unfiltered bone marrow.

This latter comment refers to the quote from Dr. O'Neill:

> "…bone marrow is unfiltered…Basically, the injection contains the "kitchen sink" and we hope that the right cells go to the right place and do the right thing."

67. First, since Dr. O'Neill was not discussing the instant specification or Applicant's argument, on what basis can it concluded that Dr. O'Neill confirms anything about the same? Nevertheless, it appears that the significance Applicant attaches to both of these comments is based on the assertion that the instant disclosure teaches the injection of unfiltered bone marrow to grow arteries and that Drs. Pollman and O'Neill are discussing the same procedure disclosed by Applicant. This assertion is not supported, as shown herein and in the record. If it were true that the specification teaches that unfiltered marrow is needed to grow an artery, such disclosure would rule out enablement of claim 409, which requires a stem cell harvested from blood. Applicant is referred to the Office action mailed 05/05/2008, paragraph 28; the Office action mailed 02/26/2009, paragraphs 14-16; and most recently, the Office action mailed 01/14/2010, paragraphs 23-28, and the present Office action wherein the Declarations of Dr. Heuser and Dr.

Lorincz under 37 CFR 1.132, filed 10/26/2010, have been considered. In the absence of further explanation or a working example, the expression "stem cells harvested from the bone marrow" does not clearly guide the skilled artisan to choose either unfractionated marrow or the mononuclear fraction. Therefore, Applicant is not justified in suggesting that subsequent disclosures involving unfiltered marrow (or any particular fraction thereof) confirm any teaching of the instant specification.

68. Next, Applicant addresses the participation of Dr. Richard Heuser, a Declarant of record in the instant case, in the published discussions:

> The answer to the PTO's irrelevant question, "Why didn't "[Dr. Heuser] enlighten his colleagues?" is straightforward. Being a patentee in his own right, Dr. Heuser fully comprehends his duty in regard to confidential information, even if the Examiner is dismissive of such duty.

69. This has been addressed in the Office action mailed 01/14/2010, paragraph 64. Applicant's confidentiality argument is not persuasive because continuing and continuation-in-part applications of the instant disclosure had been published as at the time the discussions were taking place. There may be any number of reasons why Dr. Heuser chose not to bring the instant specification into the discussion. However, the statement "One wonders why Dr. Heuser did not speak up and enlighten his colleagues" (Office action 02/26/2009, paragraph 34) is not irrelevant, as Applicant asserts, because it should cause all readers of this record to consider the impact of verbatim quotes from the instant specification might have had on the ongoing discussion, which, in turn, speaks to the guidance provided by the instant specification. The gist of Applicant's argumentation with respect to the rejection of record, especially including argumentation based on the Heuser declarations, is that the controversies under discussion have been solved or rendered trivial by Applicant's disclosure. The rejection posits that *if Applicant's*

arguments are to be accepted, then Dr. Heuser, having "read and understood" the instant specification, was in possession of information significant to the controversies under discussion. If so, Dr. Heuser could have clarified matters without divulging any confidential information by directing his colleague's attention to published disclosures. According to Applicant's arguments, Dr. Heuser could have explained that all one needs to know to grow new arteries is that "a patient's own cells" may be used to form an artery, among other possible outcomes (Specification, pages 47-48) and that "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques" can be genetically engineered to form entire organs such as a tooth, kidney, or eye, depending on the genes used (Specification, Examples 11-17). According to Applicants arguments, Dr. Heuser could have informed his colleagues that, in view of the present disclosure, they can locally inject any stem cell into any selected site in a body of a patient and predictably grow a desired artery without resorting to undue experimentation.

70. The amount of direction or guidance present and the presence or absence of working examples, are among the factors to be considered in determining whether a specification meets the enablement requirement. In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). It has been noted in the record that the present specification does not disclose even a single enabled embodiment of the claimed methods. Applicant argues with respect to working examples:

> At page 45-48, ¶¶66-68 of the Office Action, the PTO has again taken issue with the lack of working examples in the specification. Specifically, the PTO has taken the stance that the prophetic examples contained in the instant specification are inadequate for establishing a constructive reduction to practice of the claimed invention because of uncertainty expressed in the prior art as to whether cells, such as stem cells, would result in the formation of arteries.

> It has been Applicant's understanding from the beginning that prophetic disclosures are permitted under the rules, statute and case law. However, the PTO concludes, without further explanation, that the lack of actual examples "contribute significantly" to the determination of lack of enablement. It is the burden of the PTO to specifically and precisely point out why the absence of specific examples is a contributing factor.

71. This is not persuasive because the further explanation that Applicant seeks was in fact presented in paragraphs 66-68 of the previous Office action. It is herein reiterated that the fact that prophetic examples are permitted does not mean that any particular set of prophetic examples is adequate for enabling for the claims under consideration. In the present case, even the disclosed prophetic examples are not specifically directed to the claimed subject matter. The absence of specific examples is a contributing factor because a prophetic example based on predicted results rather than work actually conducted can support enablement only if the claimed results are actually predictable. Case law cited in the record confirms that chemistry, biology, medicine, and physiology have been consistently recognized as unpredictable arts. It has been established herein and in the record that Examples 11-18, 19, and 36, cited by Applicant as supporting the enablement of the instant claims, not only lack support by experimental evidence, they prophetically teach results that are totally incredible (growth of entire new organs) or contradicted by subsequent disclosures (formation of new arteries with no initial connection to preexisting vessels; direct differentiation of stem cells to all cells of arteries). It has been established herein and in the record that post-filing disclosures show that extensive experimentation has been required to achieve results that fall within the scope of the asserted claims. Regardless of how straightforward the practice of the claimed invention may be, the instant specification does not establish with any reasonable certainty how to select the cells that will form an artery, or whether administration of any of the cells mentioned in the specification

will form an artery. It is found that, when it comes to actually practicing a method, the specification does not tell the skilled artisan what to do. If there had been a working example in the specification, there would be no question of whether the specification taught the use of cells, which cells to use, how to prepare the cells (unfiltered, mononuclear fraction, or selected stem cells), how many to use, when and how to administer the cells, and whether the disclosed results are confirmed by post-filing disclosures. Every question that has been raised about the guidance in the specification might have been clarified by working examples in the specification. Instead, the instant disclosure barely makes it possible to piece the claimed generic concept together, as evidenced by the Declarations of record which show that upon reading juxtaposed excerpts of the specification (not the complete specification), together with claims that were not present in the application as filed, the Declarants of record have been willing to say: "The disclosures referenced in above Paragraph ... of the specification relate to using a growth factor for promoting the growth of soft tissue, and more specifically, to a method of using a cell, such as a stem cell, to grow soft tissue, such as an artery" (emphasis added)." A disclosure that merely makes it possible to piece the claimed generic concept together is not the same as an enabling disclosure.

72. Continuing with the subject of working examples, Applicant argues:

> Applicant notes the PTO's gratuitous justification for the granting of the Isner and Kornowski patents. It is certainly not Applicant's position that these patents should not have been granted. Rather Applicant has pointed to certain facts contained in such patents that were not an obstacle to allowance. Applicant also notes that the PTO has attempts to distinguish between the prophetic examples of Applicant and the admittedly prophetic examples of Kornowski on the basis that Kornowski had animal studies. Such purported distinction is meaningless when it is considered that prophetic examples are permitted under current law.

73. To clarify, the previous Office action did not include any "justification for the granting of the Isner and Kornowski patents", much less a "gratuitous justification". No justification is required, or even appropriate in this context, for patents that have already been granted. Applicant had argued, and apparently still argues, that the Isner '887 and Kornowski '832 patents were allowed with claims to treatment of humans that were supported only by prophetic examples and, therefore, the prophetic examples of the instant case should also be considered sufficient. Applicant's argument is not persuasive for reasons fully explained in paragraph 67 of the previous Office action. The examples in the patents, which show results of animal studies, are not "admittedly prophetic" because they are based on work actually performed and results actually achieved. This is not a "purported distinction" as it is the definition of a working example; See MPEP 2164.02. The sufficiency of the evidence is determined on a case-by-case basis. The instant specification provides no evidence comparable to that in the Kornowski '832 patent upon which to base a judgment. The fact that animal studies are not perfectly predictive of human responses does not support the argument that science can be ignored altogether and the instant claims should be considered enabled when they are supported by no data at all.

74. Beginning on page 61, Applicant again addresses the Declarations of Dr. Heuser and Dr. Lorincz. Most of Applicant's present arguments are repetitive of those which have been addressed in paragraph 69 of the previous Office action.

75. Applicant again relies on the conclusion reached by the Declarants, reproduced here:

> I note that the disclosures referenced in above Paragraph 4 relate to using a growth factor for promoting the growth of soft tissue, and more specifically, to a method of using a cell, such as a stem cell, to grow soft tissue, such as an artery. [emphasis added]

76. Such conclusion is derived from the specification at pages 47-48. No Declarant stated that any part of the specification directs the skilled artisan to select any specific type or source of stem cells to specifically grow an artery—they merely state that the referenced disclosures "relate to" the general topic of using a cell to grow soft tissue. One pieces together the general concept of the claimed method by selecting "stem cell" from the genus of cells and "artery" from the genus of soft tissues. It is evident, however, that the sweeping generalizations in the specification could be interpreted as teaching almost anything. The Declarants could just as easily have opined that "the disclosures referenced in above Paragraph" relate to using a stem cell from the blood to grow a kidney, to using a dedifferentiated skin cell to grow pancreatic islets, or to using any sticky cell to grow an entire new heart. Thus, the Declarants conclusion that the specification relates to a method of using a stem cell to grow an artery requires no further rebuttal because even if it is accepted it does not support enablement of the claimed methods. It is maintained that disclosure that merely makes it possible to piece the claimed generic concept together is not the same as an enabling disclosure.

77. Applicant further argues:

> Contrary to the PTO's position, Applicant's evidence of enablement is supported by more than Declarants' conclusory statements. Declarants identify and rely upon facts, i.e., specific portions of the disclosure in the instant specification which support their conclusions that one skilled in the art would be able to make and use the claimed invention.

78. This is not persuasive because it has been shown in the record that the "specific portions of the disclosure" cited by Applicant and the Declarants contain numerous statements that cannot be reasonably characterized as "facts". Examples 11-17 do not set forth credible procedures to produce the results asserted within the examples, and they do not even mention growth of an artery as recited in the instant claims. Bone marrow stem cells are not known to have the

capability of differentiation and morphogenesis to form an entire organ, such as an eye, kidney or tooth, even under the influence of an electric spark or an expressed gene such as Aniridia or MSX-1. The prediction that "if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro" (specification p.48, lines 13-15) is, at best, mere speculation when the source of stem cells is a mixed population of bone marrow cells and the organ under consideration is a new artery; the Ziegelhoeffer reference would suggest that this prediction is simply not born out. There is no evidence that new arteries are formed from structures that initially form in the absence of any connection to preexisting arteries as taught in prophetic Examples 18 (p.54), 19 (p.56) and 36 (p. 62); in fact post-filing evidence teaches the contrary (Buschmann, Augustin; of record). The general statement that organs and/or tissues can be formed utilizing the patient's own cells on page 47 of the specification can be accepted as fact, but even this is tainted by exemplification of a "patient's own cells" as a skin cell(s) is removed from the intraoral lining of a cheek and taken through a speculative and frankly incredible process of dedifferentiation and redifferentiation. The sections of the specification cited in the declarations have been thoroughly considered, along with the entire disclosure, herein and in the record. Applicant is again referred to paragraphs 23-47, especially paragraphs 31-40 of the previous Office Action. Thus, the Declarants' conclusory statement as to the ultimate legal conclusion of enablement, has been given due consideration and found to be opinion that is not supported by underlying facts.

79. Applicant, who has previously broached the subject of ad hominem argumentation, seeks to overcome the evidence of record by asserting that such evidence does not exist and by arguing

that the Examiner is not qualified to do anything other than uncritically accept Applicant's and Declarants' opinions:

> In the absence of critical analysis, the PTO appears to be relying solely upon its opinion rather than assessing weight to the objective evidence proffered in the Declarations. PTO Examiners, not being skilled persons in the medical art, must give weight to these expert opinions rather than substitute the opinion of the PTO. See In re Neave, 370 F.2d 961, 152 USPQ 274, (CCPA 1967). (page 63)
>
> Finally, the PTO states that the sections of the specification cited in the declarations have been thoroughly considered. However, no analysis or rebuttal to the expert opinions has been presented. Rather the mere opinion of the present PTO Examiner, a non-expert in the medical art appears. This is error because the declarations provide evidence that rebuts any prima facie case of obviousness [sic-non-enablement?] established by the PTO. (p.64)
>
> That the present PTO Examiner lacks knowledge of this routine conversion commonly used by skilled medical practitioners is not dispositive of this issue. (p.51)

80. In this regard, Applicant's repeated citation of In re Neave, 370 F.2d 961,152 USPQ 274; (CCPA 1967) is not persuasive. In that case, the declaration evidence relied on a subjective determination of color based on visual inspection and estimation. The court found that the ability to make this determination was an acquired skill of the expert and that determinations of this sort were routinely viewed as decisive and not mere opinion by persons of skill in the art. Thus, the court did not hold that all expert opinions should be accepted as fact, but only that in this particular case, the apparently subjective opinion of the expert should be accept as fact because this was the accepted practice in the art. The court further found that the same skill would not be possessed by the examiner or the Board. Therefore, the expert's opinion was accepted as evidence of an unexpected result and the obviousness rejection written by the examiner and sustained by the Board was overturned (In re Neave, at 280). In the present case, Applicant asserts that the Declarants possess knowledge that is not possessed by the Examiner but

Applicant cannot point to any decisive facts cited by Declarants that are not available to the Examiner. In the present case, nothing is based solely on the Examiner's opinion. Each finding that a Declarant's opinion is not persuasive to overcome the rejection of record is supported by facts and references. The rejection can only be overcome by countervailing facts, not by the mere assertion that the Examiner is not qualified to formulate an argument.

81. Applicant' comparison of the instant case to in re Wands, (Argument p. 64-65) is identical to the argument previously presented on pages 47-48 of the Appeal Brief filed 08/20/2009. Said argument has received due consideration in paragraph 70 of the previous Office action.

82. Finally, Applicant takes issue with the citation of Genentech v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 (1997) in the previous Office action:

> The PTO's citation and reliance on the Genentech at page¶71 of the Office Action is inapt. Applicant has consistently pointed out wherein the specification provides guidance for carrying out the claimed invention. The PTO seems to be under the impression that all that is required to support an enablement rejection is to repeat by rote case law without significant analysis establishing precedent visa vis the evidence in chief relied on for a prima facie case.

83. In response to Applicant's assertion, it is noted that like the present case, the question in Genentech was whether a patent contained sufficient detail concerning the practice of the claimed method. Genentech made the argument that the knowledge of one skilled in the art was sufficient to provide all of the missing information. Applicant has made the same argument; it has been argued herein and previously that in the present case the only Wands factor weighing in favor of enablement is the level of skill in the art, which is relatively high. Thus, there are ample parallels between the present case and Genentech. The court held that Genentech's arguments were focused almost exclusively on the level of skill in the art and ignored the essence of the

enablement requirement. "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute an enabling disclosure. Reasonable detail must be provided in order to enable members of the public to understand and carry out the invention" (Genentech v. Novo Nordisk A/S at 1005). The rejection of record has stated that, "While evidence of a fully developed clinical procedure is not required for a patent, the notion that the claimed new result, artery growth, can be achieved using old materials (bone marrow stem cells) and old methods (injection), was indeed "a germ of an idea" at the time the instant application was filed. The instant specification does not even clearly enunciate this germ of an idea, let alone provide an enabling disclosure of how to make and use the claimed invention." While the entire prosecution history of the present case could be cited in support of this conclusion, the Declarations of Dr. Heuser and Dr. Lorincz provide a useful example. The Declarants stated that the referenced disclosures for the specification "relate to" using a cell to grow soft tissue. One pieces together the general concept of the claimed method by selecting "stem cell" from the genus of cells and "artery" from the genus of soft tissues. As noted herein and in the record, even after this concept is formed, the specification provides no further guidance or example directed to the claimed method. As noted herein and in the record, the specification never once explicitly teaches that one should inject stem cells into a selected site and thereby grow a desired artery. Thus, the descriptor "vague intimations of general ideas that may or may not be workable" precisely describes the notion of growing a desired artery by locally injecting stem cells, even when the teachings of the specification and the state of the art at the time the application was filed are taken into account. It is easy to predict that if one injects cells into a body, something

will grow therefrom; it might even be an artery—even tumors have arteries. Such a prediction however, does not meet the legal standard for enablement. As stated in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

84. The rejection of record has given careful consideration to the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the level of skill in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. It has been acknowledged that the level of skill in the art is high. However, the remaining factors indicate that the each of the claims under consideration must be rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Double Patenting

85. Provisional rejection of claims 403 and 407-412 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 161-164 and 172-174 copending Application No. 10179589 is maintained for reasons of record. Applicant's statement

regarding submission of an appropriate Terminal Disclaimer upon an indication of allowable subject matter is acknowledged.

Conclusion

86. No claim is allowed.

87. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, Ph.D., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571)272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Daniel C Gamett/
Examiner, Art Unit 1647

/David S Romeo/
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